Small Cell Lung Cancer: Novel Approaches 2019

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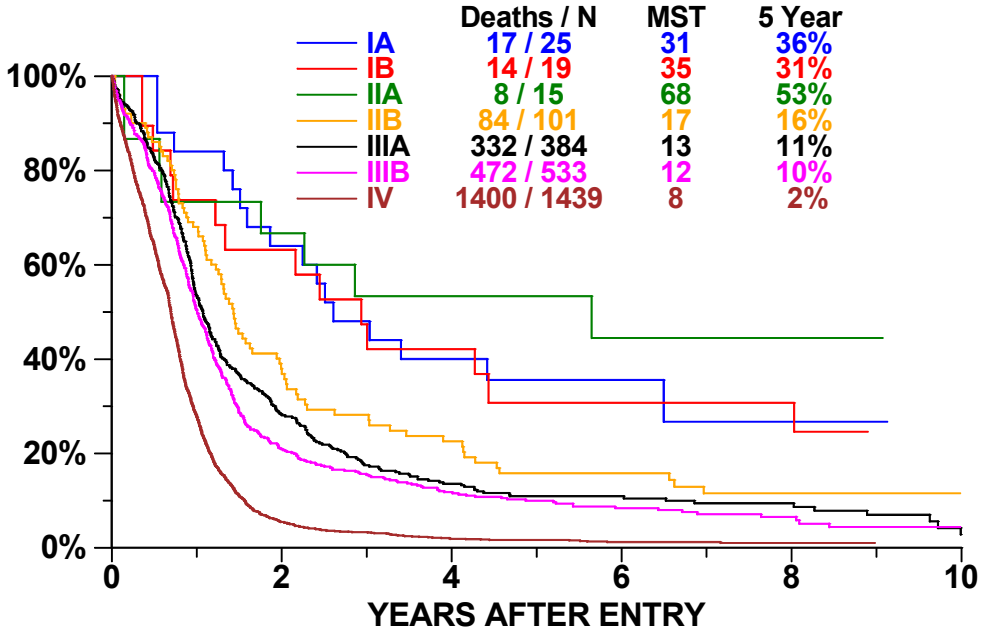
Disclosures

- **Institutional Research Grants: Roche-Genentech, Novartis, Merck**
- **Consultant/Advisory Board: AstraZeneca, Celgene, CellMax, FujiFilm, Roche-Genentech, Guardant Health, Inivata, IO Biotech, Lilly, Merck, Samsung Bioepis**

Small Cell Lung Cancer:

High Proliferation Rate, Early Dissemination, Initial Chemo- Radiation-sensitivity → Refractory Disease

- High propensity for early systemic dissemination
  - Over 70% present with extensive stage disease
  - Up to 65% relapse with brain metastases
  - Over 85% succumb within 1 year of relapse



Shepherd et al: J Thorac Oncol 2007

Demographic, Biologic, Clinical & Therapeutic Differences between SCLC & NSCLC

Feature	SCLC	NSCLC
Incidence	Decreasing	Increasing
Association with Smoking	Universal	Highly Variable
Mutational Load	High	Variable
Biologic Diversity (Histologic & Molecular)	~More Uniform	Distinct Subtypes
Growth Kinetics	~Rapid	Variable
Early Metastases	Universal	Variable
Sensitivity to DNA-damaging chemotherapy (1st line)	High	Variable
Sensitivity to Radiotherapy	High	Variable
Advances in Therapy ~15 years	Few Advances	Dramatic Advances

Current Status:
Systemic Therapy of Extensive SCLC

- Platinum/Etoposide (PE) has been the standard for first-line therapy in the U.S. for ~20 years, **but this has now changed**
- In **1st line therapy**, new regimens consistently failed to surpass PE in Phase III comparisons until
  - Over 20 new chemotherapeutic & biologic agents failed
  - Dose intensification including BM transplantation failed
  - **Checkpoint Immunotherapy + PE set new standard of care**
- In **2nd line therapy**, a number of chemotherapeutic agents are active in "platinum-sensitive" patients, but the "platinum-refractory" subset fares poorly
  - **Despite modest ORRs & short PFS, 2nd line CPIs result in some long term survivors**
- Additional studies evaluating novel molecular-targeted agents in first- and second-line therapies of SCLC are needed
- Advances but Controversial:
  - Prophylactic Cranial Irradiation (PCI) is reported to be beneficial but is controversial
  - "Consolidation" thoracic RT is reported to be beneficial but is controversial

Investigation of Chemotherapy Agents in SCLC

Agent	Response Rate in Phase II: 1st line/2nd line	Results (1st line in combination with Platinum)
Paclitaxel	~35%/~25%	Negative Phase III trial (Niell et al)
Gemcitabine	~25%/14%	Phase II: not promising (Hesketh et al)
Topotecan	?/~18%	"Positive" Phase III: but not adopted (Heigener et al)
Irinotecan	~35%/~25%	Conflicting results of Phase III trials (Noda; Lara; Hanna)
Pemetrexed	?	Negative Phase III trial (Socinski et al)
Amrubicin	~40%	Negative Phase III 2nd line trial (Jotte et al) Negative Phase III 2nd line trial (Kotani et al)

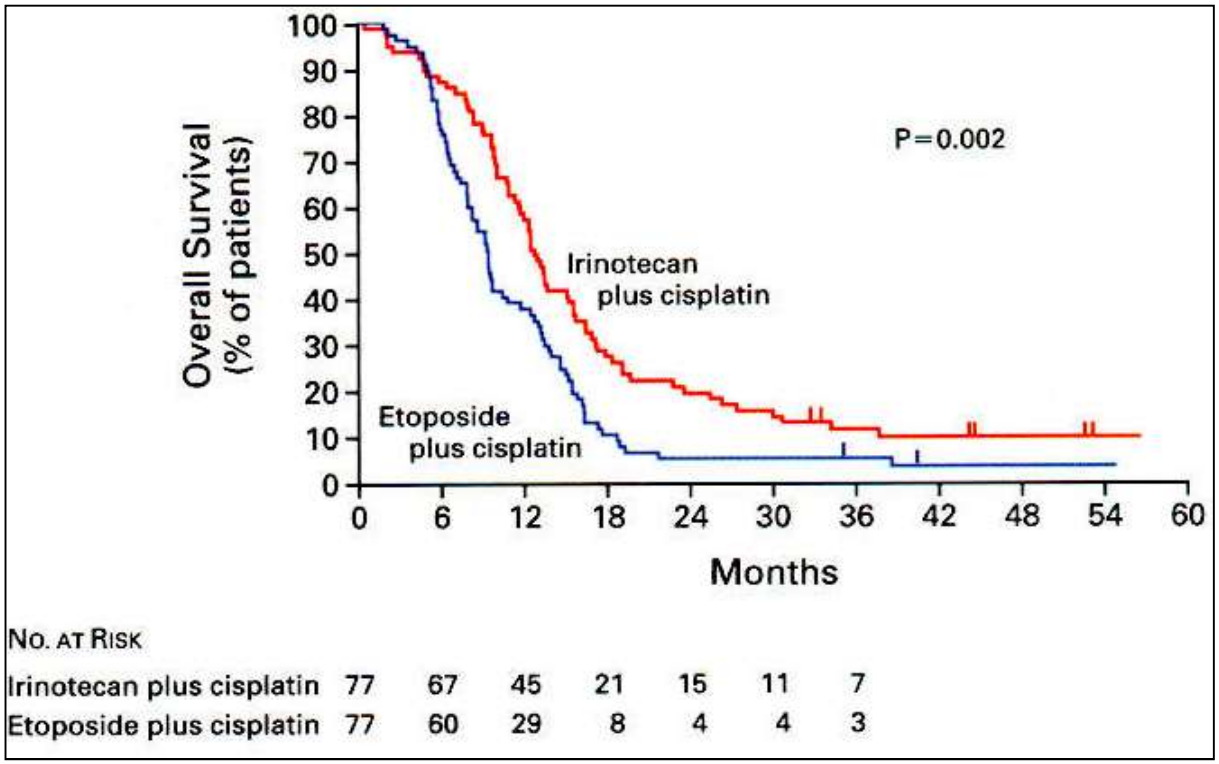
JCOG 9511: Phase III Trial in E-SCLC

Stratify
PS (0, 1, 2)

RANDOMIZE

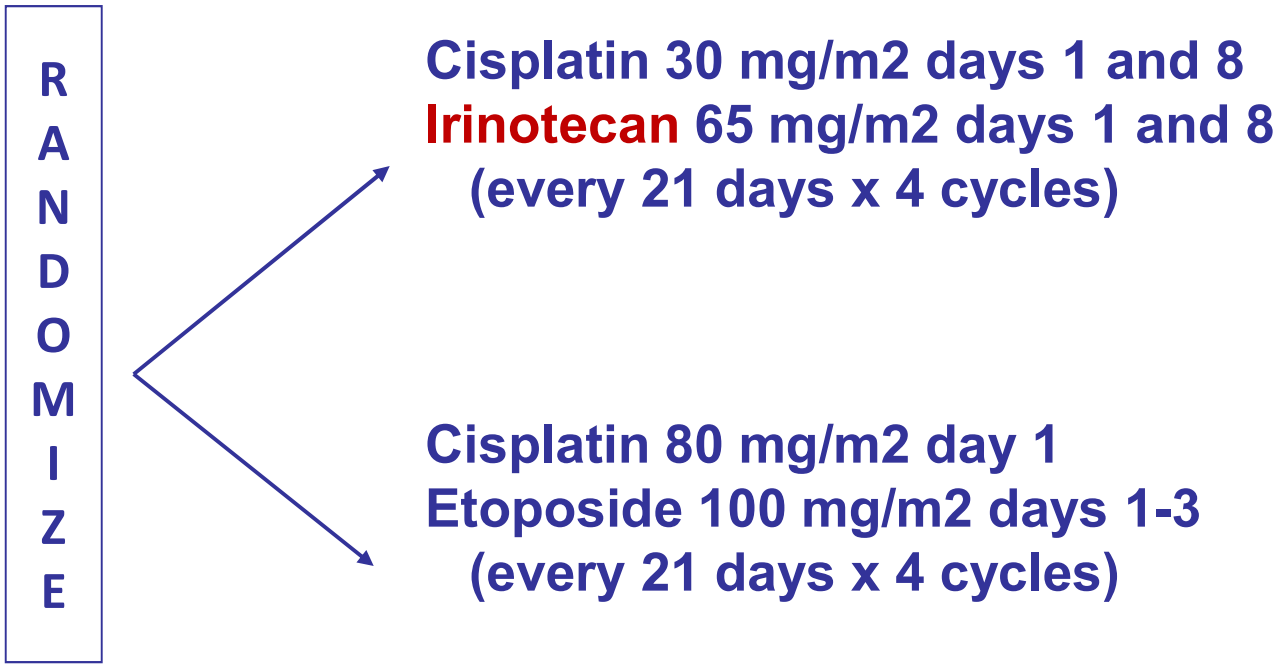
→ Irinotecan 60 mg/m^2 d1,8,15
Cisplatin 60 mg/m^2 d1 — Q4wk x 4

→ Etoposide 100 mg/m^2 d1-3
Cisplatin 80 mg/m^2 d1 — Q3wk x 4



Noda: NEJM, 2002

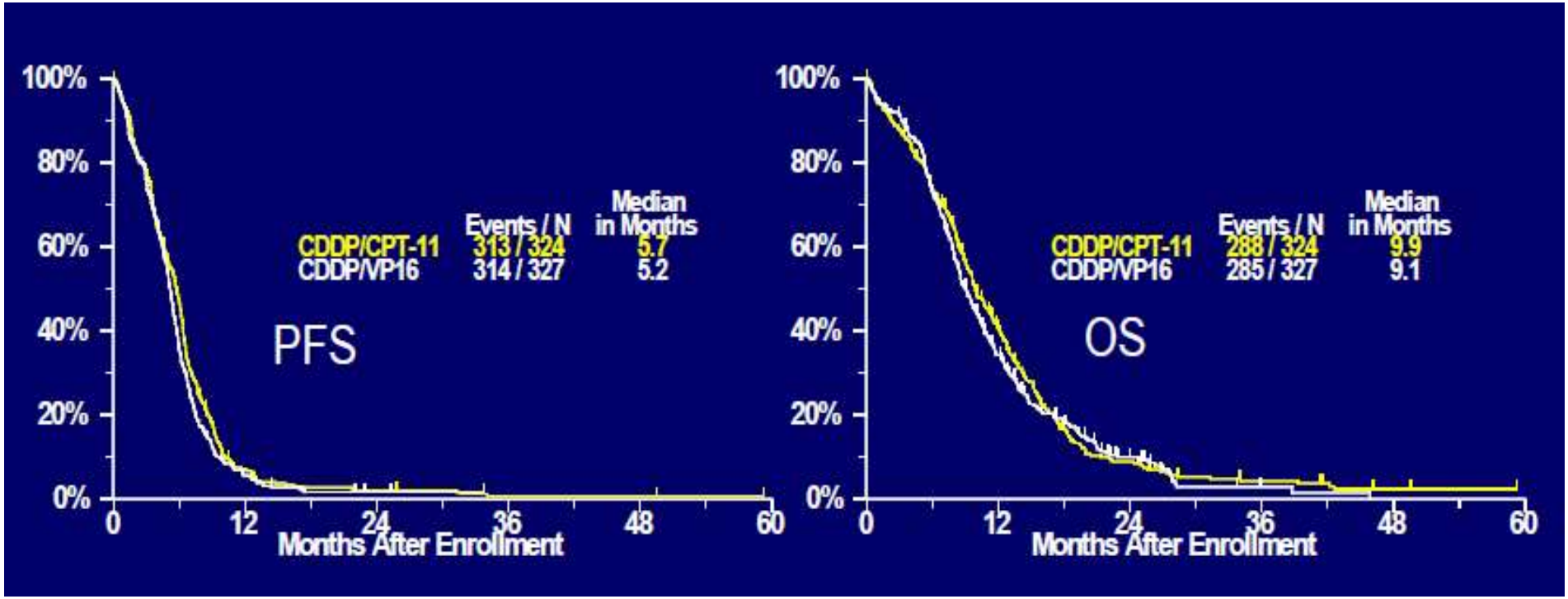
SWOG 0124:
Cisplatin/Irinotecan (PI) vs Cisplatin/Etoposide (PE)



- Hypothesis: Results of S0124 will differ from J9511 due to population-related pharmacogenomics for Irinotecan disposition in Japanese vs U.S. populations
- Identical drug dose schedules for J9511 & S0124
- Unique Aspect of S0124
  - Comparative efficacy of J9511 & S0124 using “common arm” approach
  - Comparative Toxicity of J9511 & S0124: patient level data

SWOG 0124:
Cisplatin/Irinotecan (PI) vs Cisplatin/Etoposide (PE)

	PI	PE	p-value
• Response	60%	57%	0.56
• PFS (mos)	5.7	5.2	0.07
• OS (mos)	9.9	9.1	0.71



Lara et al: JCO, 2009

Comparative Toxicities of JCOG 9511 versus SWOG 0124: Cisplatin/Irinotecan "common arm"

≥ Grade 3	(PI) Cisplatin/Irinotecan	
	J9511 (n=75)	S0124 (n=278)
Neutropenia	49 (65%)*	88 (32%)
Leukopenia	20 (27%)**	48 (17%)
Anemia	21 (28%)*	16 (6%)
Diarrhea	12 (16%)	51 (18%)

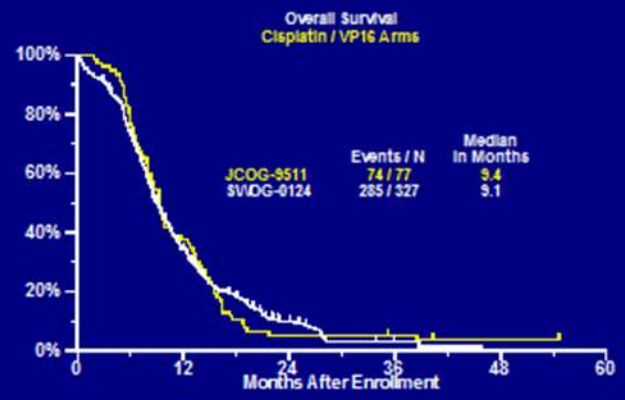
* p<0.0001 **p=0.02

Japanese patients have more toxicity with the same treatment regimen & dose delivery

Lara et al: JCO, 2009

Comparative Efficacy of JCOG 9511 versus SWOG 0124

Overall Survival by Trial:
***Cisplatin / Etoposide* (VP-16) Arm**



J9511 and S0124 have similar OS in the control Cisplatin/Etoposide "common arm"

Overall Survival by Trial:
***Cisplatin / Irinotecan* (CPT-11) Arm**

J9511 demonstrates longer OS compared to S0124 in the Cisplatin/Irinotecan "common arm"

S0124 did not confirm results of J9511
Efficacy of Irinotecan greater in Japanese patients
Toxicity is also greater in Japanese patients
Population-related Pharmacogenomics may have influenced results

Lara et al: JCO, 2009

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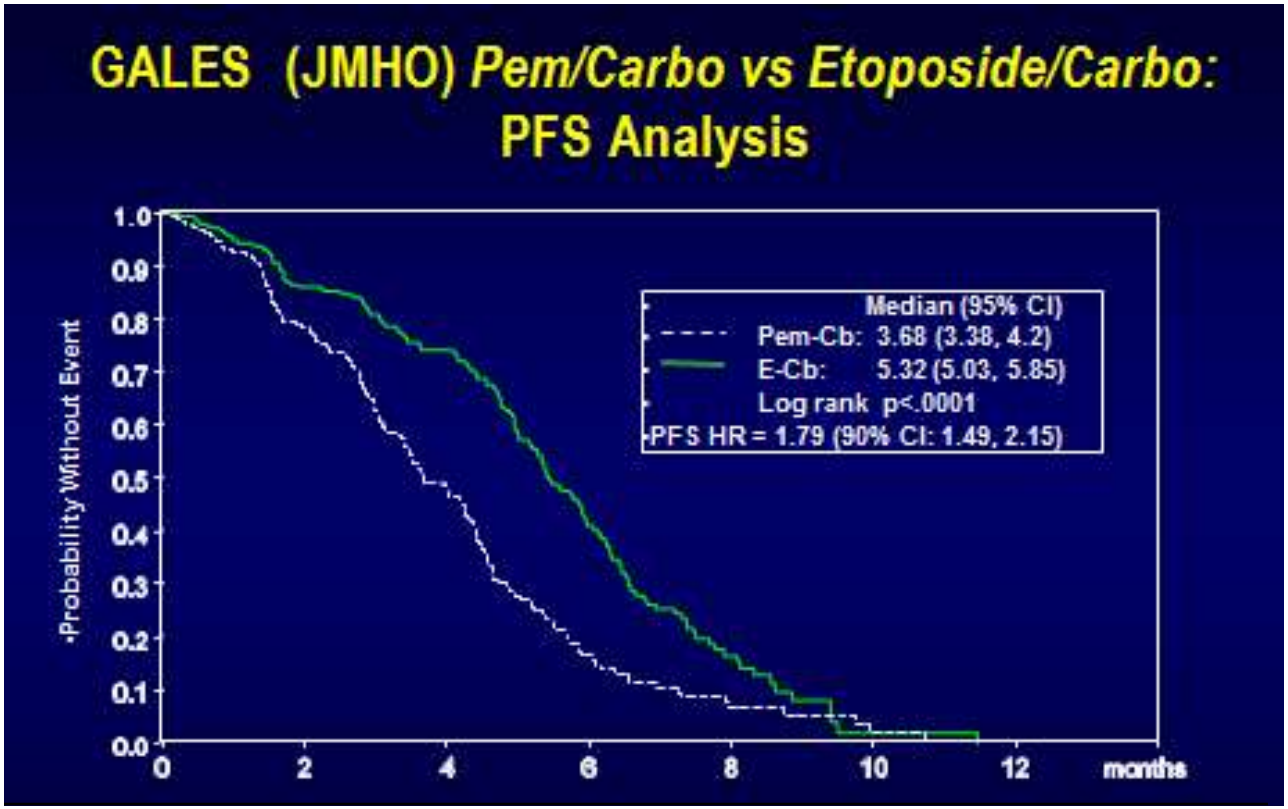
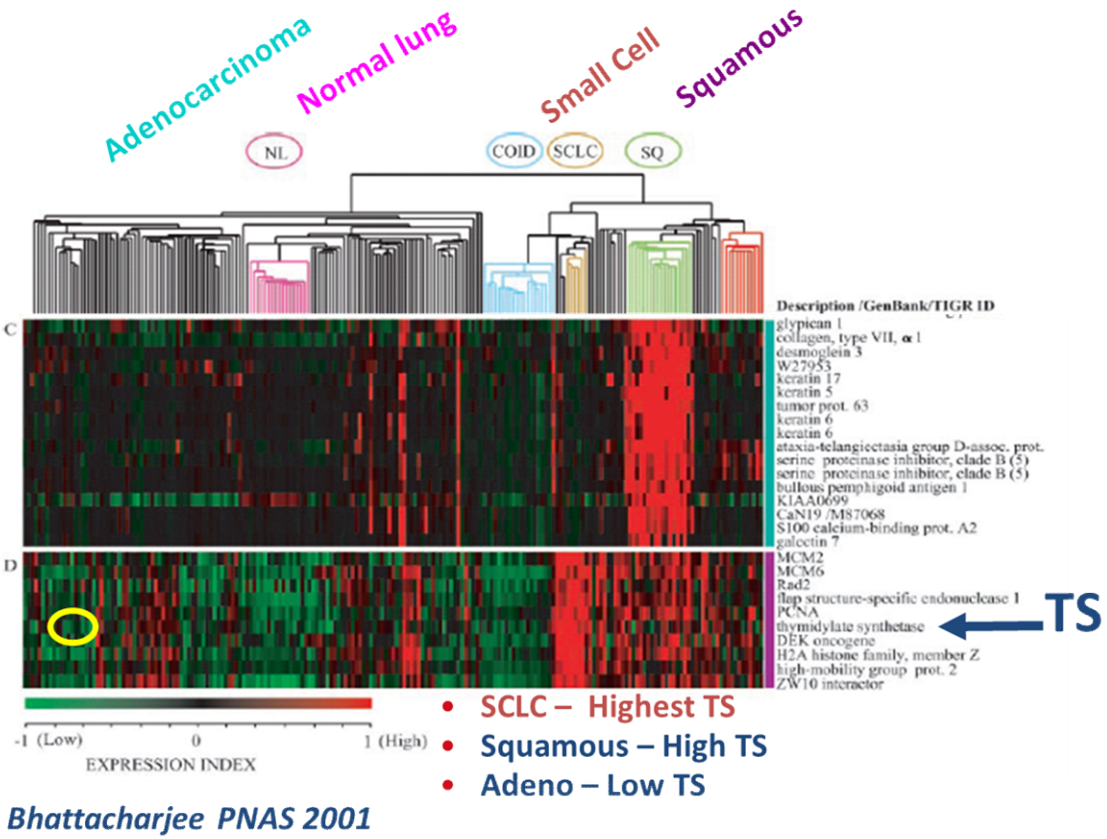
Lessons Learned: Pemetrexed (GALES) Phase III trial in Extensive SCLC



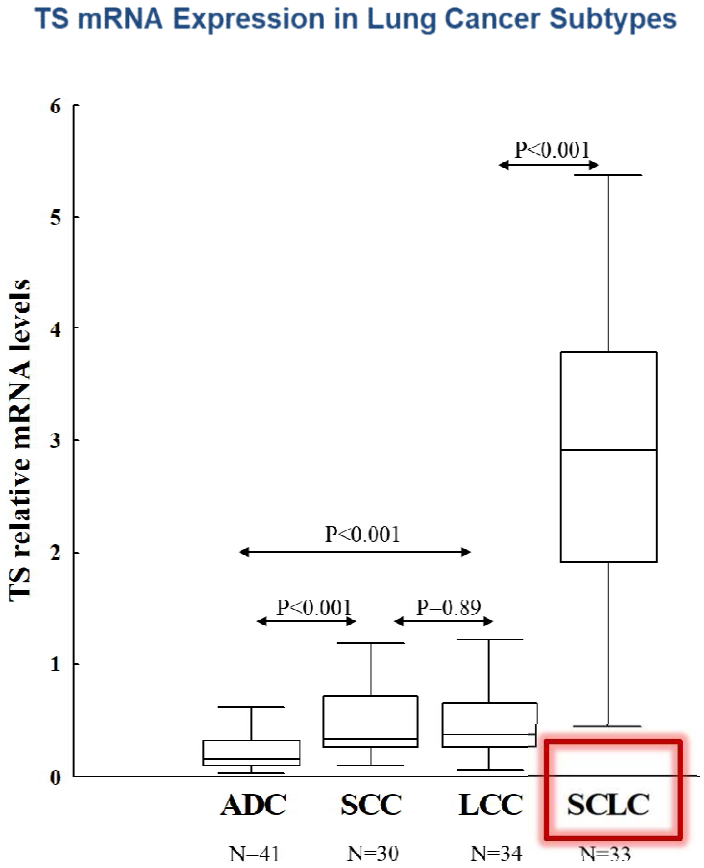
	Pem/Carbo (N=453)	Etoposide/Carbo (N=455)
Median OS (mo) (95% CI)	8.1 (7.3, 9.1)	10.6 (9.7, 11.6)

Socinski et al: ASCO 2008; Smit et al: ASCO 2009

Thymidylate Synthetase (TS) Expression in Lung Cancer



Bhattacharjee PNAS 2001



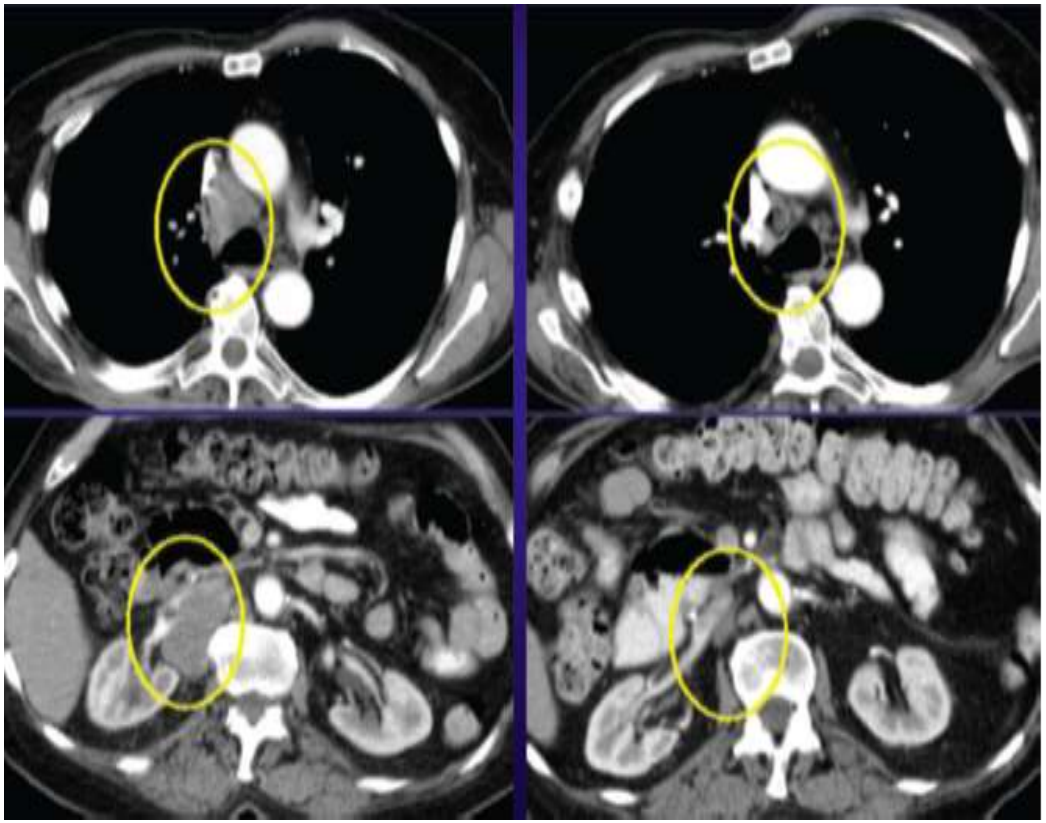
Ceppi et al: Cancer 2006

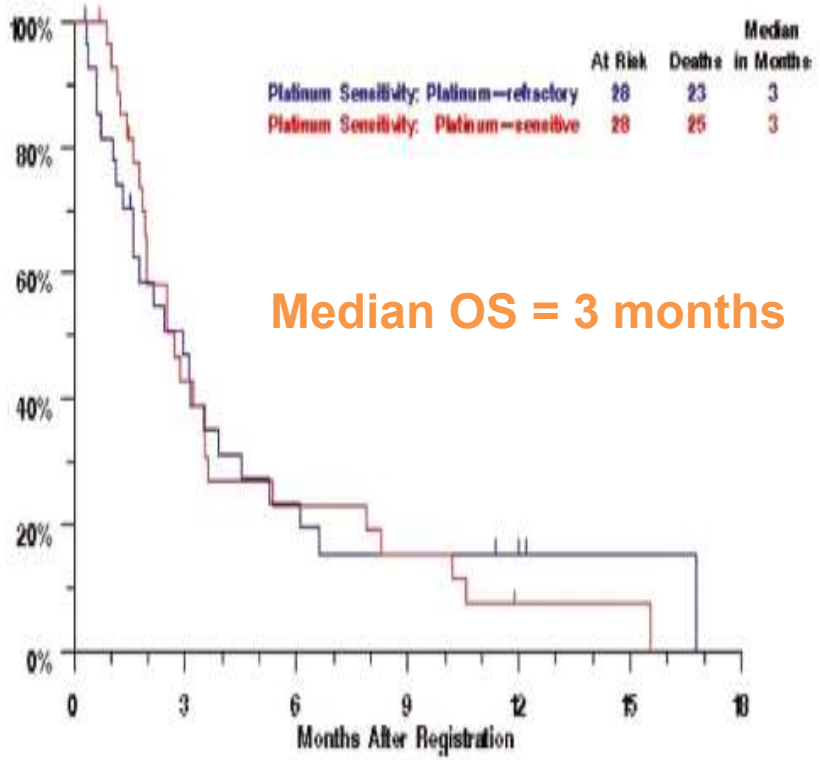
Investigation of "Targeted Therapies" in Extensive Stage SCLC

Selected Agents	Target(s)	Results
Imatinib (Johnson et al)	KIT, SCF	Inactive
Bec2/BCG (Giaccone)	GD3 ganglioside	Negative Phase III trial
Bortezomib (PS-341) (Lara et al)	Proteasome	Insufficient activity
Sorafenib (Gitliz et al)	VEGFR	Insufficient activity PR: PlatSens: 5% PlatRef: 2%
Vandetanib (ZD6474) (Arnold et al)	EGFR/VEGFR	HR 1.43 vs Placebo for OS
ABT263 & Obatoclax (Rudin et al; Langer et al)	Bcl-2	Insufficient activity
Aflibercept (VEGF-Trap or AVE0005) S0802 (Allen)	VEGF	Modest activity added to topotecan
ABT888 + PE vs PE (Belani)	PARP	Negative

Bortezomib (PS-341) in Relapsed or Refractory Extensive Stage Small Cell Lung Cancer: A Southwest Oncology Group Phase II Trial (S0327)

Primo N. Lara, Jr., MD,† Kari Chansky, MS,‡ Angela M. Davies, MD,* Wilbur A. Franklin, MD,§ Paul H. Gumerlock, PhD,* Perry P. Guaglianone, MD,‖ James N. Atkins, MD,¶ Nichole Farneth, BS,* Philip C. Mack, PhD,* John J. Crowley, PhD,* and David R. Gandara, MD*†*





Lara, JTO 2006

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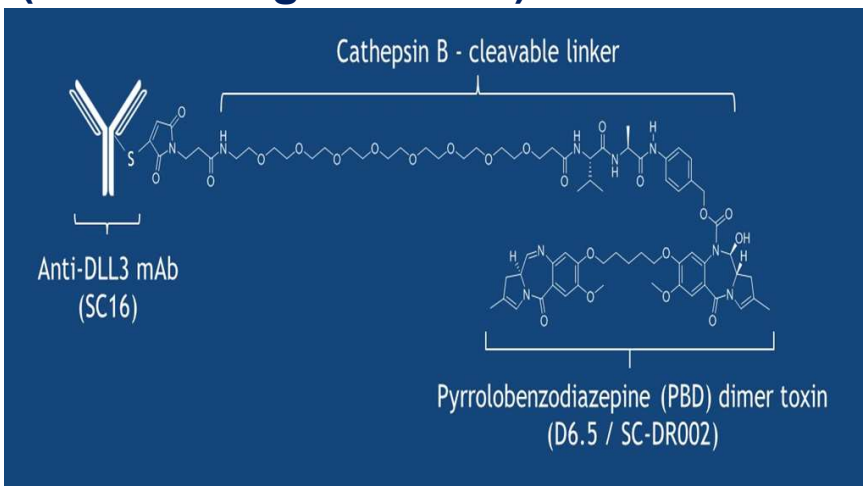
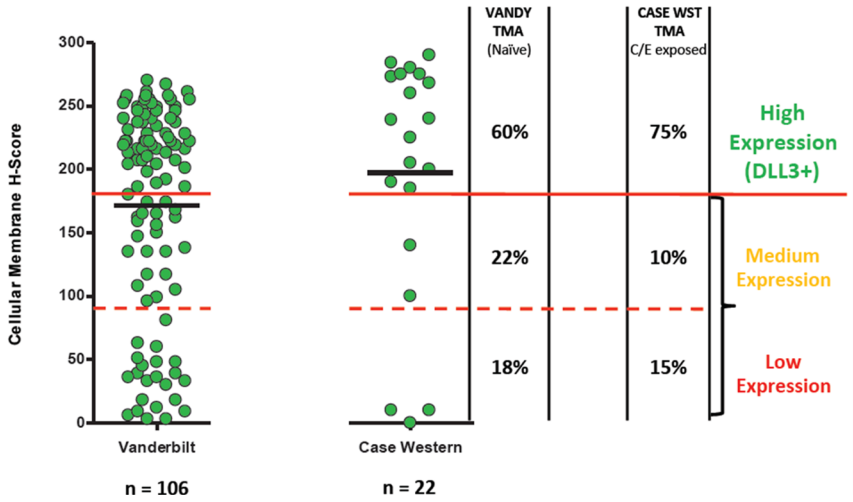
ABT888 + PE vs PE (Belani)	PARP	Negative
Rova-T	DLL3 (Notch path)	TRINITY (Insufficient Activity)

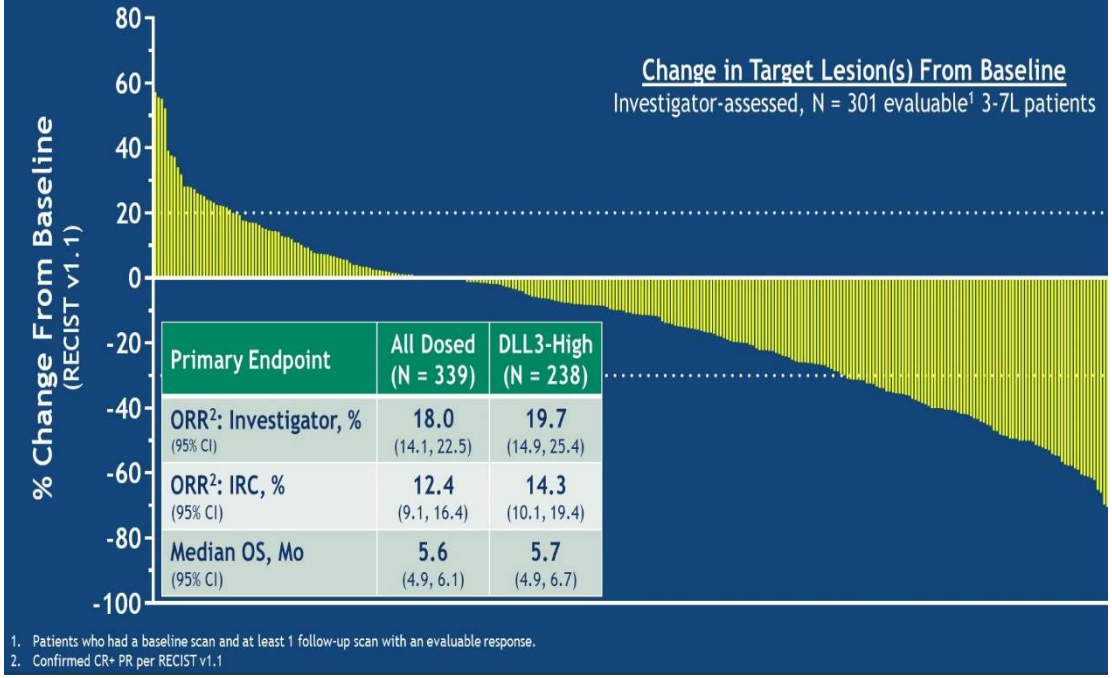
TRINITY: Phase II Trial of Rova-T (a DLL3-targeted ADC) in E-SCLC



DLL3 Expression is highly expressed in SCLC



TRINITY: Primary Endpoint Analyses



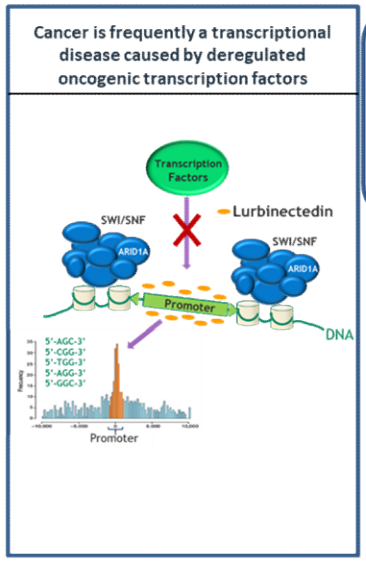
Primary Endpoint	All Dosed (N = 339)	DLL3-High (N = 238)
ORR[2]: Investigator, % (95% CI)	18.0 (14.1, 22.5)	19.7 (14.9, 25.4)
ORR[2]: IRC, % (95% CI)	12.4 (9.1, 16.4)	14.3 (10.1, 19.4)
Median OS, Mo (95% CI)	5.6 (4.9, 6.1)	5.7 (4.9, 6.7)

1. Patients who had a baseline scan and at least 1 follow-up scan with an evaluable response.
2. Confirmed CR+ PR per RECIST v1.1

TEAEs	All Patients, N = 339	
	Any n (%)	Drug-Related n (%)
Any AEs	335 (99%)	308 (91%)
Serious AEs	170 (50%)	100 (30%)
Grade 3+ AEs	179 (53%)	134 (40%)
AEs with fatal outcome	34 (10%)	10 (3%)
AEs resulting in:		
Discontinuation	24 (7%)	16 (5%)
Interruption	32 (9%)	29 (9%)
Dose reduction	33 (10%)	32 (9%)

Carbone et al: ASCO18

Lurbinectedin in SCLC: Phase 2 study in 2nd-line therapy



SCLC patients
Performance score 0–2
1 prior chemotherapy
Prior IO allowed
Adequate organ function
CNS metastasis excluded

Lurbinectedin 3.2 mg/m², 1h IV, q3w

≥2 responses in first 15 patients* → Enrol up to 100 patients

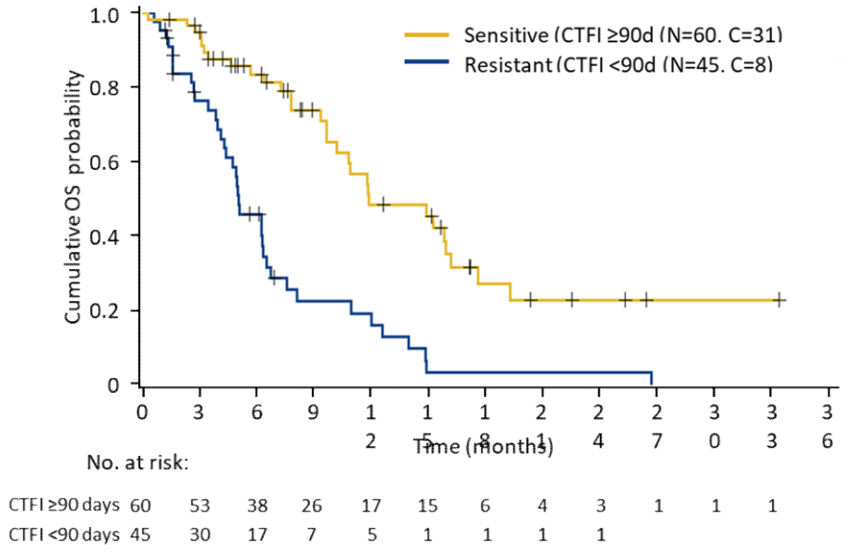
Primary objective: ORR per RECIST v1.1

Statistical assumptions
Null hypothesis: ≤15% get a response (p≤0.15)
Alternative hypothesis: ≥30% get a response (p≥0.30)
Statistical power 95%
≥23% of confirmed responses needed to reject the null hypothesis

	Overall (N=105)
ORR, % (95% CI)	35.2 (26.2–45.2)
Best response, n (%)	
PR (confirmed)	37 (35.2)[b]
SD	35 (33.3)
PD	28 (26.7)
Not evaluable	5 (4.8)
Disease control rate, % (95% CI)	68.6 (58.8–77.3)

	Resistant: CTFI <90 days (n=45)	Sensitive: CTFI ≥90 days (n=60)
ORR, % (95% CI)	22.2 (11.2–37.1)	45.0 (32.1–58.4)
Best response, n (%)		
PR (confirmed)	10 (22.2)[c]	27 (45.0)[c]
SD	13 (28.9)	22 (36.7)
PD	18 (40.0)	10 (16.7)
Not evaluable	4 (8.9)	1 (1.7)
Disease control rate, % (95% CI)	51.1 (35.8–66.3)	81.7 (69.6–90.5)

Overall survival in Sensitive and Resistant populations

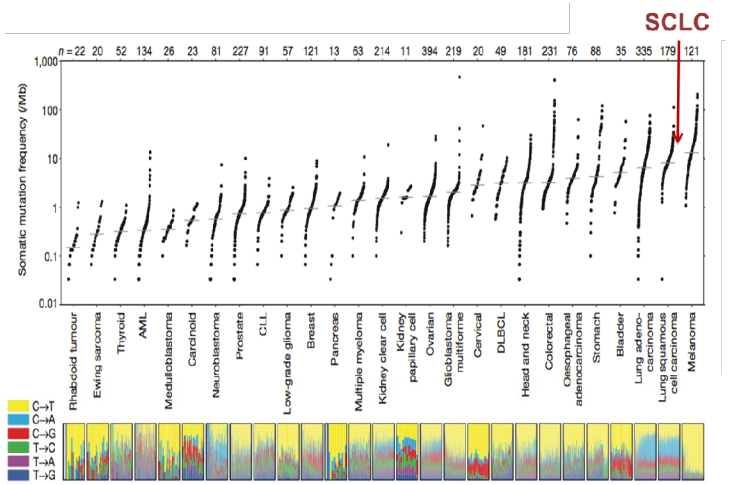


	n	Median OS, mo (95% CI)	OS at 12 mo, % (95% CI)
All	105	9.3 (6.3-11.8)	34.2 (23.2-45.1)
Resistant (CTFI <90d)	45	5.0 (4.1-6.3)	15.9 (3.6-28.2)
Sensitive (CTFI ≥90d)	60	11.9 (9.7-16.2)	48.3 (32.5-64.1)

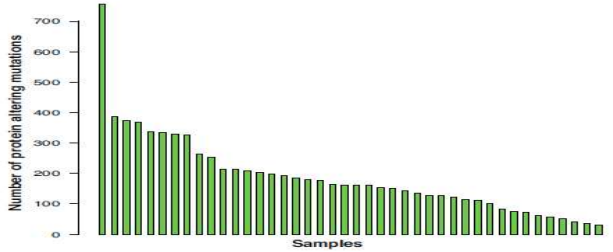
Paz-Ares LG, et al. ASCO 2019. Abstract 8506.

Rationale for Checkpoint Immunotherapy (CPI) in SCLC

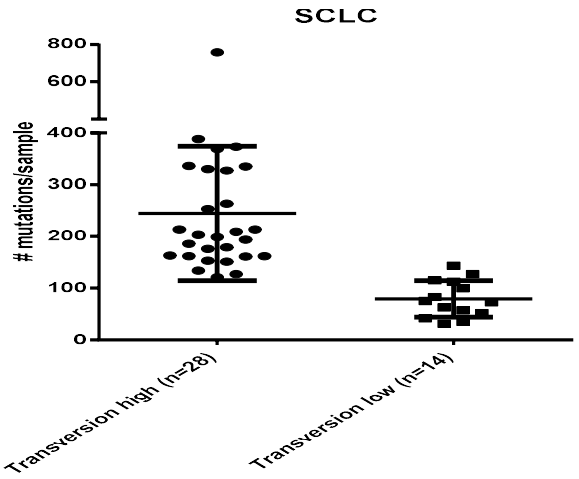
- SCLC ranks among the highest of all tumor types in terms of # of mutations/Mb of DNA



- Extraordinarily high numbers of somatic mutations in some patients



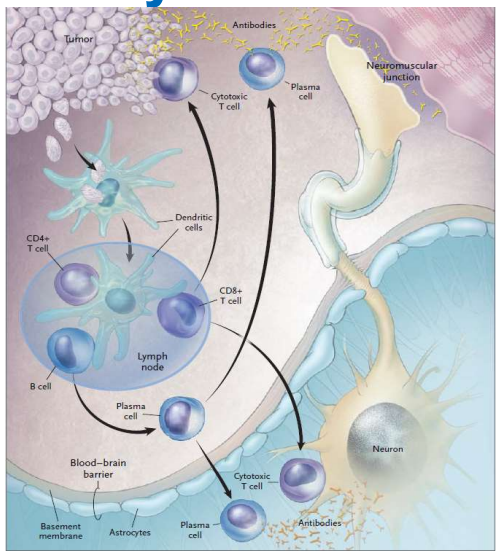
- Mutations are most commonly G to T transversions
  - Reflective of DNA-damaging tobacco carcinogens
  - Strongly neoantigenic



Rudin C, et al. *Nature Genetics*. 2012;44:1111.
Peifer M, et al. *Nature Genetics.* 2012;44:1104.
George J, et al. *Nature*. 2015;524:47.

SCLC associated with Immunogenic Effects

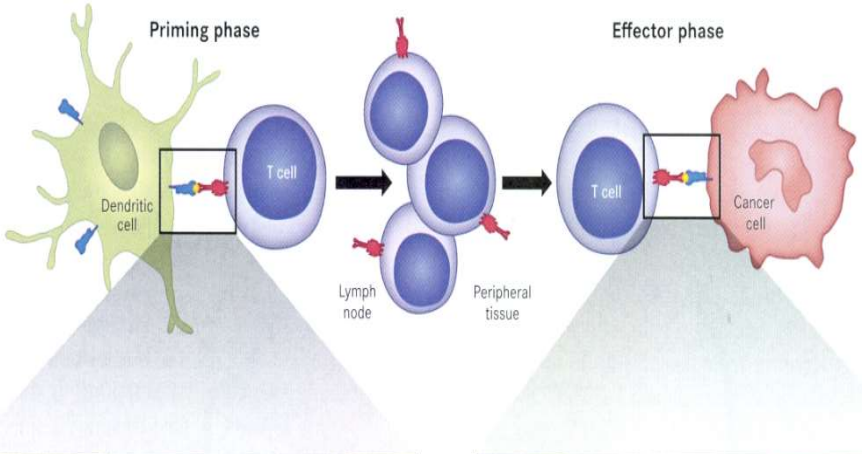
- Subset of SCLCs elicit CD4-dependent antibody and CD8 T-cell responses against neuronal antigens expressed by the tumor
  - Associated with immune-mediated paraneoplastic syndromes



- SCLC patients with neurologic paraneoplastic syndromes and anti-Hu autoantibodies have an improved response to therapy and prolonged survival

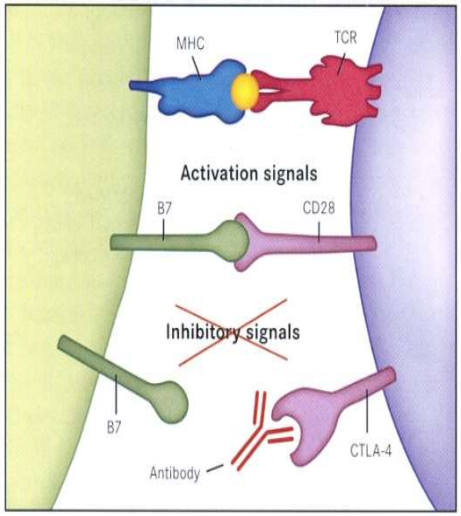
Darnell RB & Posner JB. NEJM. 2003;349:1543.
Brahmer JR & Pardoll DM. Cancer Immunol Res. 2013;1:85.
Roberts WK, et al. J Clin Invest. 2009;119:2042.

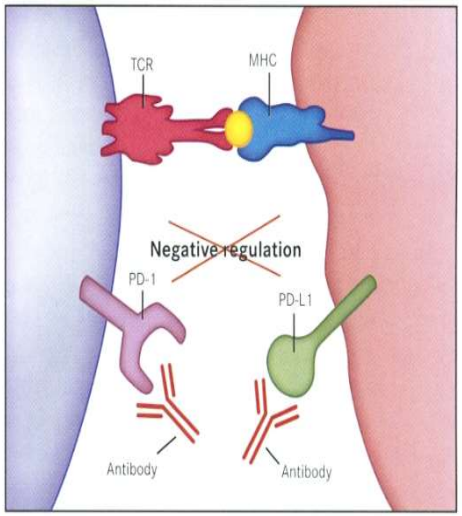
Checkpoint Immuno-Therapeutics



CTLA-4

Inhibitors:
Ipilimumab
Tremilimumab



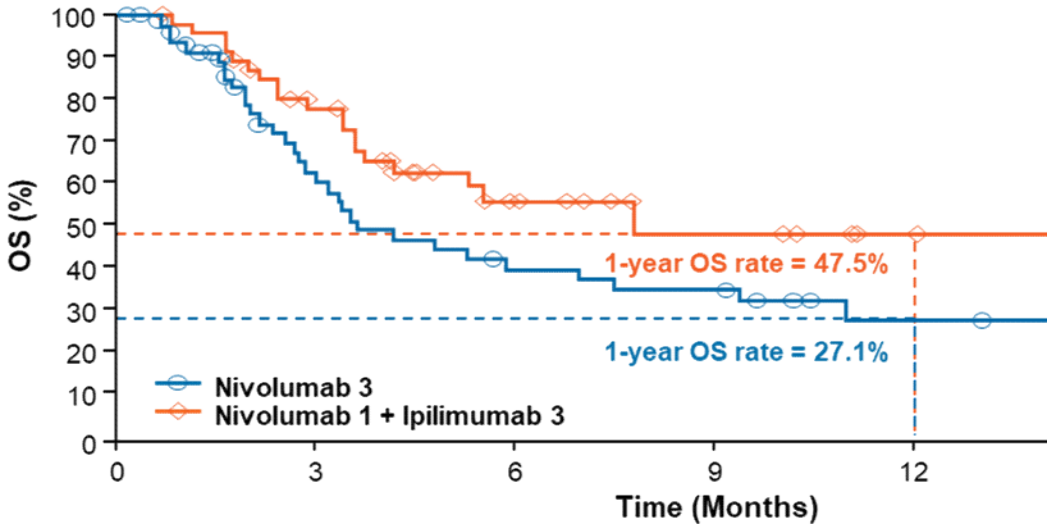


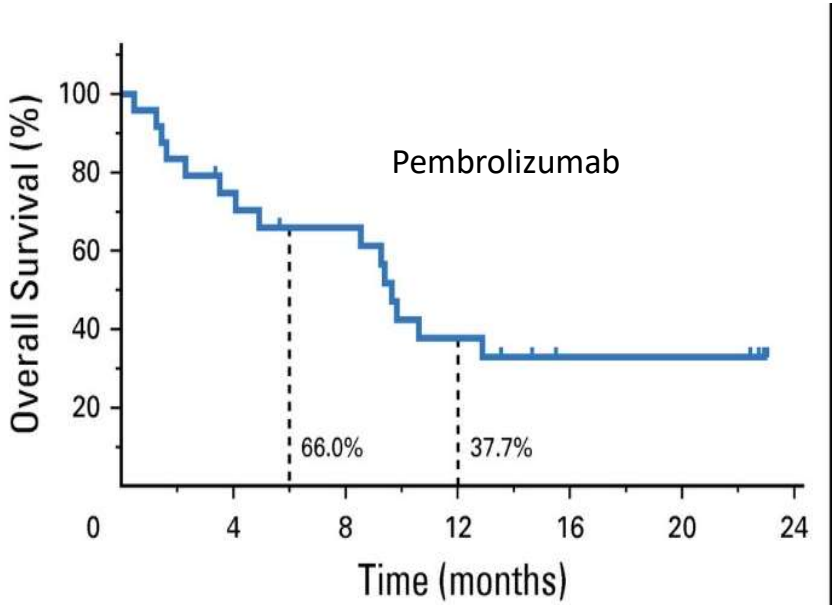
PD-1/PD-L1

Inhibitors:
Nivolumab
Pembrolizumab
Atezolizumab
Durvalumab
Avelumab

CheckMate 032 and Keynote 028 in previously treated E-SCLC

Overall survival





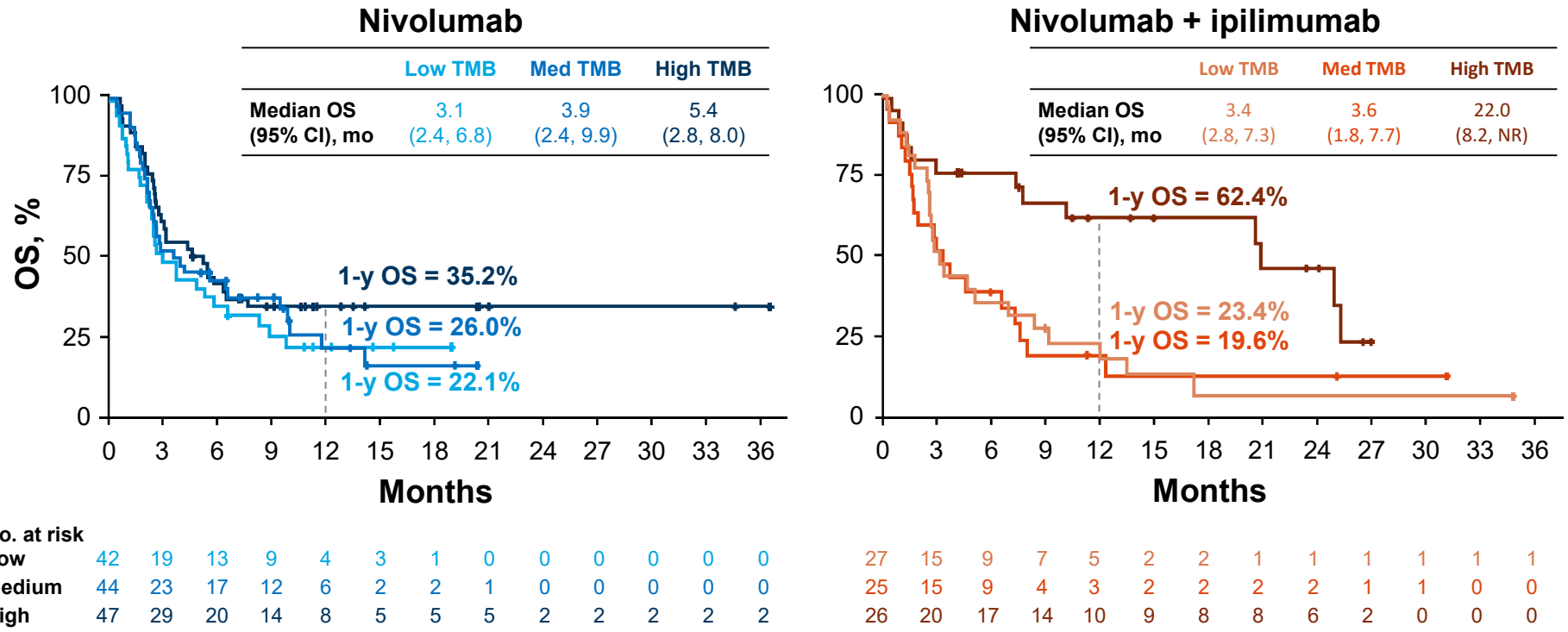
NCCN Guidelines have all 3 options: Nivo, Nivo+ipi, and Pembro

FDA approved nivolumab for 3rd line therapy in Aug 2018; pembrolizumab in June 2019

Hellman et al: JCO 2017 & E. Calvo; ESMO, 2015

OS by Tumor Mutation Burden Subgroup

CheckMate 032 Exploratory TMB Analysis Nivo ± Ipi in Previously Treated SCLC



No. at risk													
Low	42	19	13	9	4	3	1	0	0	0	0	0	0
Medium	44	23	17	12	6	2	2	1	0	0	0	0	0
High	47	29	20	14	8	5	5	5	2	2	2	2	2

	27	15	9	7	5	2	2	1	1	1	1	1	1
	25	15	9	4	3	2	2	2	2	1	1	0	0
	26	20	17	14	10	9	8	8	6	2	0	0	0

Median (95% CI) OS, overall TMB-evaluable population: 3.9 (2.8, 6.1) months for nivolumab and 7.0 (3.2, 8.8) months for nivolumab + ipilimumab; NR = not reached

Hellman et al: JCO 2017

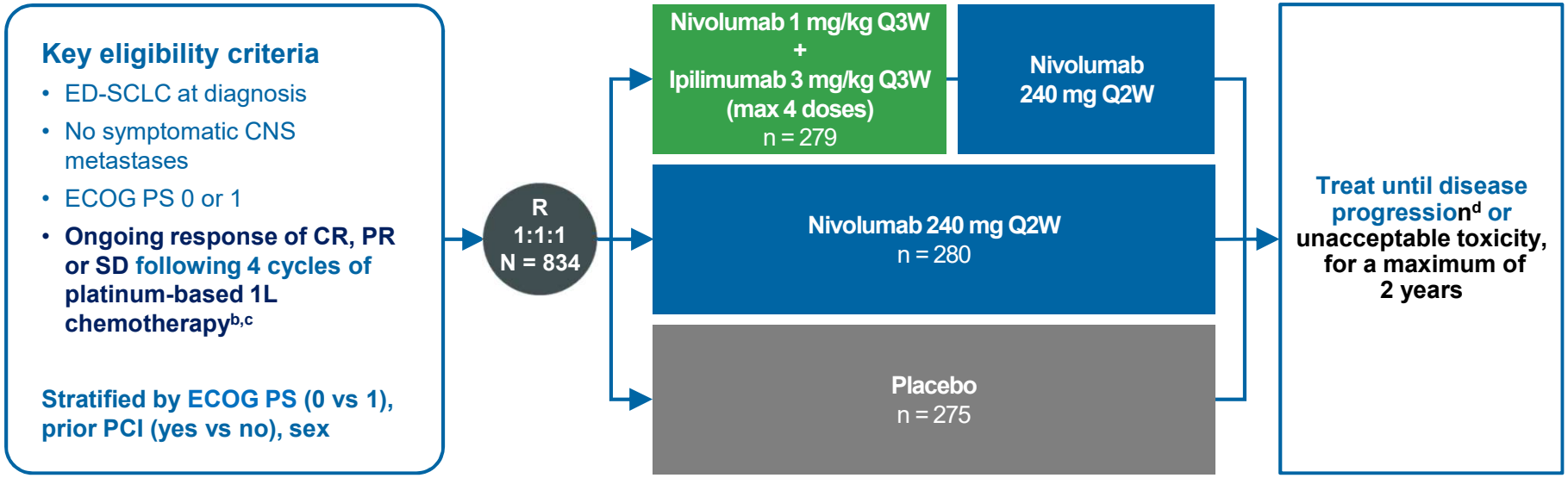
CM032: Treatment-related AEs in ≥5% Patients

	NIVO (n = 40)		NIVO1 + IPI3 (n = 47)	
	Any Grade, %	Grade 3-4, %	Any Grade, %	Grade 3-4, %
Total TRAEs	53	15	77	34
Fatigue	18	3	21	0
Diarrhea	13	0	23	9
Nausea	10	0	13	2
Vomiting	3	0	9	4
Pruritus	8	0	19	2
Rash	3	0	21	4
Rash maculopapular	0	0	13	4
Hypothyroidism	5	0	15	0
Hyperthyroidism	3	0	13	0
AST increased	5	0	4	0
Amylase increased	3	3	6	2
Lipase increased	0	0	11	6
Pneumonitis	5	0	2	2

Limbic encephalitis of grade 2 occurred in 2 pts (NIVO, n = 1; NIVO 1 + IPI 3, n = 1) and resolved under immunosuppressive treatment. One pt (NIVO, n = 1) had grade 4 limbic encephalitis with minor response to immunosuppressive treatment. One fatal case of **Myasthenia Gravis** in combination therapy arm

S. Antonia et al: ASCO 2015 and Hellman et al: JCO 2017

CheckMate 451 Study Design: Maintenance Nivo or Nivo/Ipi



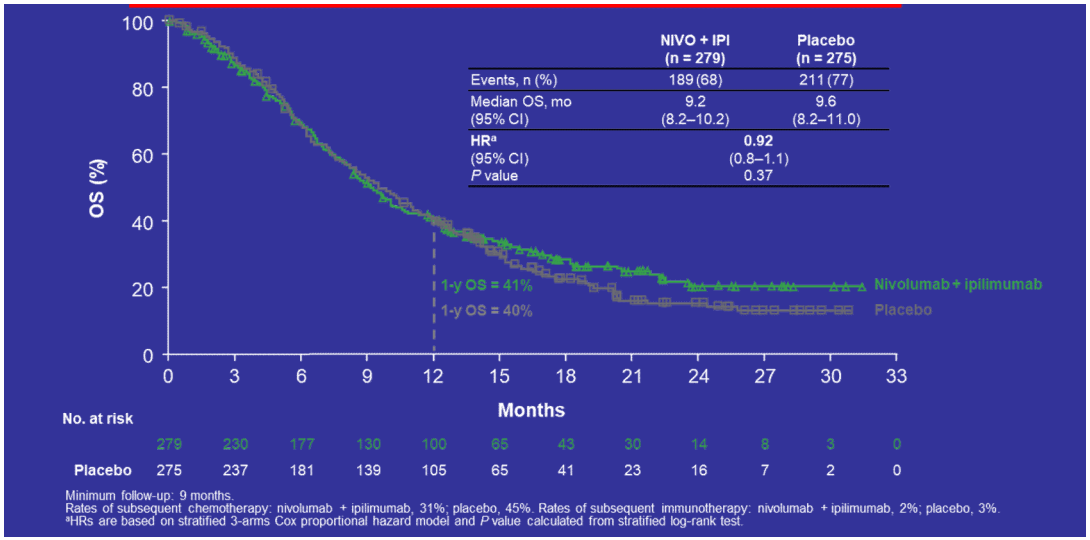
- **Primary endpoint**:
  - OS: nivolumab + ipilimumab vs placebo
- **Secondary endpoints:**[e]
  - OS: nivolumab vs placebo
  - PFS: nivolumab + ipilimumab vs placebo[f]
  - PFS: nivolumab vs placebo[f]
- **Exploratory endpoints:**
  - ORR and DOR
  - Safety and tolerability

PCI, prophylactic cranial irradiation.
Database lock: November 12, 2018; minimum follow-up: 9 months.
[a]NCT02538666; [b]Patients receiving only 3 cycles of chemotherapy due to toxicity were eligible, if they had an ongoing PR or CR after the third cycle; [c]All patients were randomized ≤ 9 weeks from the last dose of 1L chemotherapy, or ≤ 11 weeks for those receiving PCI or whole brain radiotherapy; [d]Patients could be treated beyond progression under protocol-defined circumstances; [e]Secondary endpoints to be tested hierarchically if primary endpoint met; [f]Per blinded independent central review.

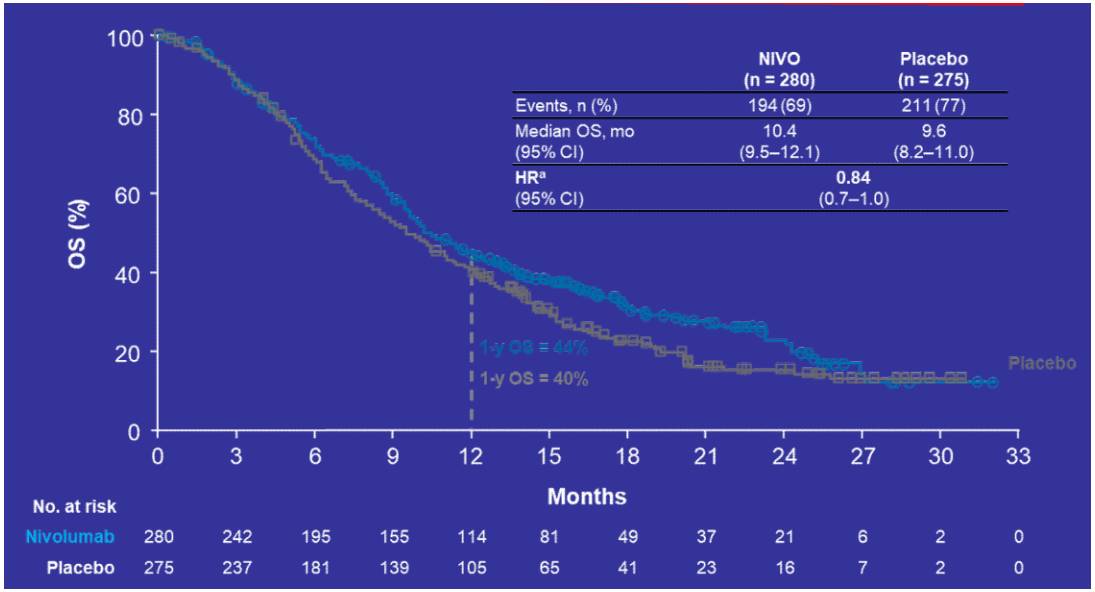
Owonikoko et al: ELCC 2019

CheckMate 451: Phase III trial of Nivo or Nivo-Ipi vs Placebo Maintenance Therapy

CM 451:
OS of Nivo + Ipi vs Placebo



CM 451:
OS of Nivo vs Placebo



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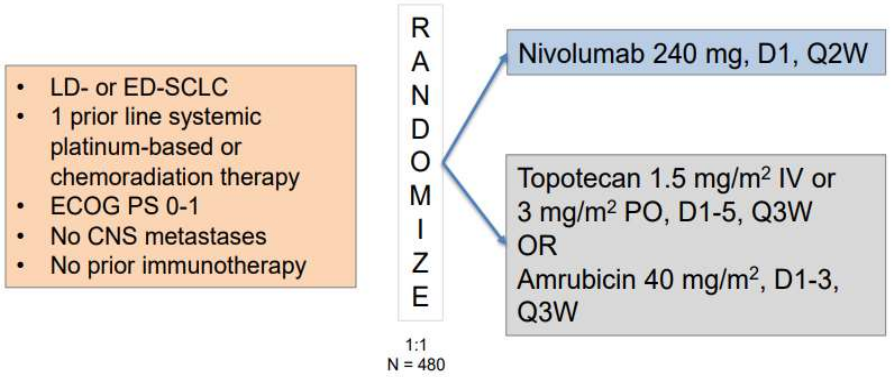
CheckMate 331: Nivo vs. Topotecan in 2nd line ES-SCLC

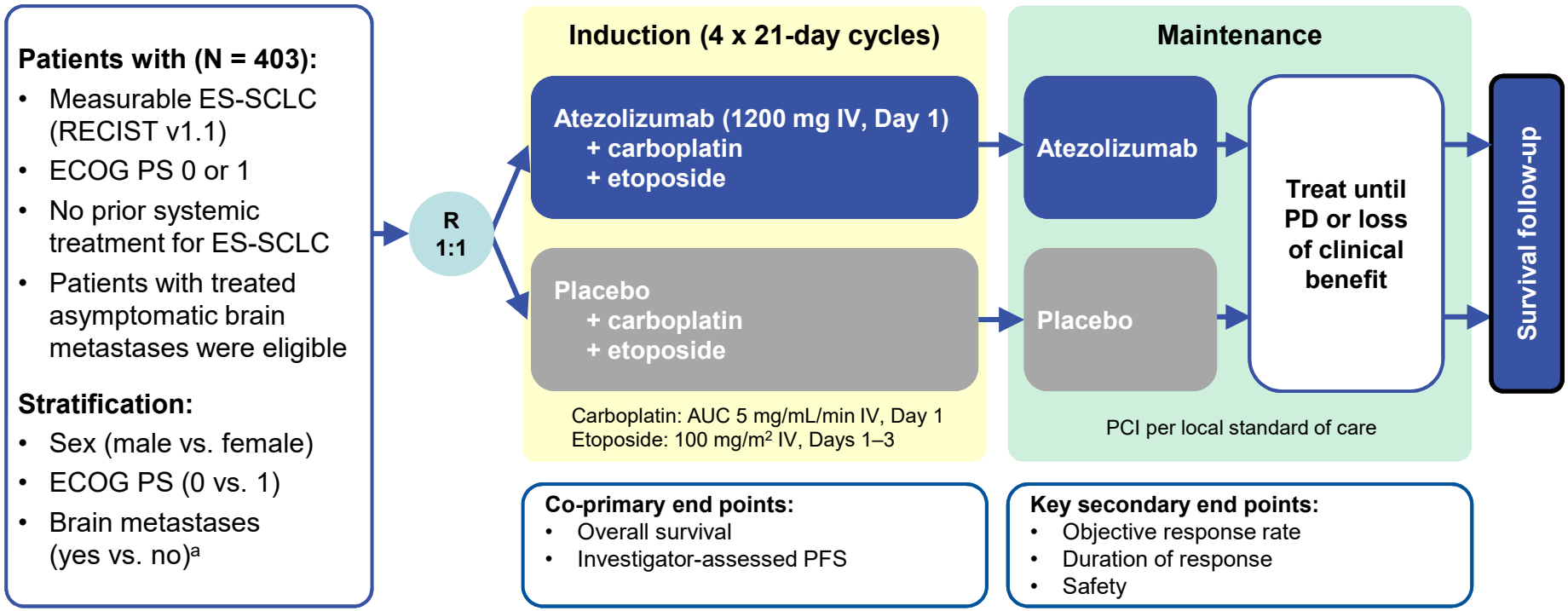


- Co-primary endpoint: OS
- Secondary endpoints: ORR, PFS
- Primary completion date: March 2018

	Nivo (n = 284)	Topotecan (n = 285)
Overall survival		
Median, months (95% CI)	**7.5 (5.7–9.2)**	**8.4 (7.0–10.0)**
HR (95% CI)	**0.86 (0.72–1.04)** **P = 0.11[c]**	
1-year OS rate, % (95% CI)	**37 (31–42)**	**34 (29–40)**
Progression-free survival		
Median, months (95% CI)	**1.4 (1.4–1.5)**	**3.8 (3.0–4.2)**
HR (95% CI)	**1.41 (1.18–1.69)**	
1-year PFS rate, % (95% CI)	**11 (8–15)**	**10 (7–14)**
Objective response rate, n (%)	**39 (14)**	**47 (16)**
Odds ratio (95% CI)	**0.80 (0.50–1.27)**	
Duration of response		
n events/n responders (%)	**28/39 (72)**	**43/47 (92)**
DOR-Median, months (95% CI)	**8.3 (7.0–12.6)**	**4.5 (4.1–5.8**

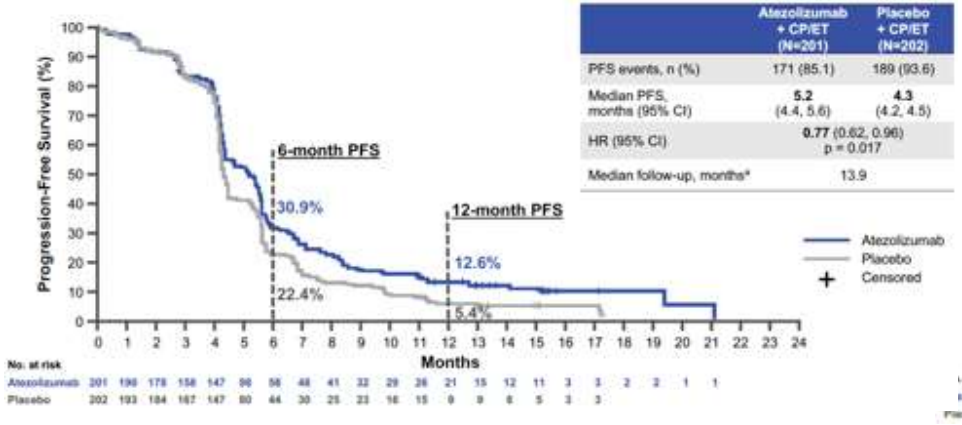
Reck et al: ESMO IO 2018

IMpower133: Global Phase 1/3, double blind, randomized, placebo-controlled trial evaluated atezolizumab + carboplatin + etoposide in 1L ES-SCLC

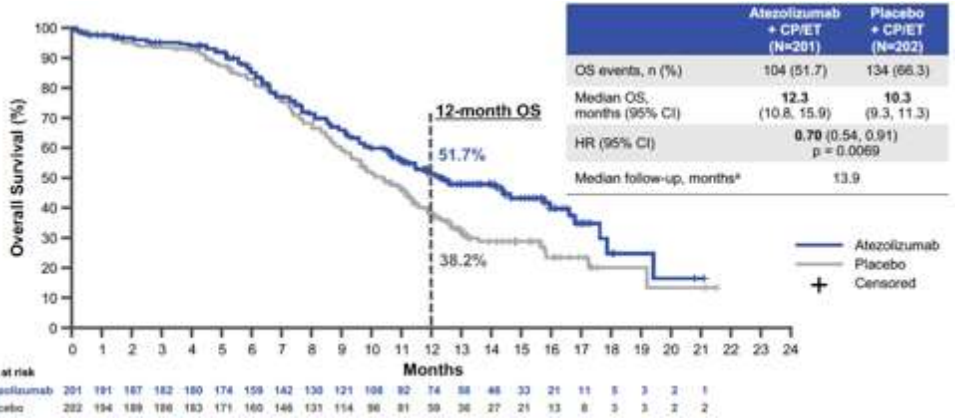


[a] Only patients with treated brain metastases were eligible. ECOG PS, Eastern Cooperative Oncology Group Performance Status; IV, intravenous; PCI, prophylactic cranial irradiation; PD, progressive disease; PFS, progression-free survival; R, randomized; RECIST, Response Evaluation Criteria In Solid Tumors.

Horn et al: N Engl J Med 2018



	Atezolizumab + CP/ET (N=201)	Placebo + CP/ET (N=202)
PFS events, n (%)	171 (85.1)	189 (93.6)
Median PFS, months (95% CI)	5.2 (4.4, 5.6)	4.3 (4.2, 4.5)
HR (95% CI)	0.77 (0.62, 0.96) p = 0.017	
Median follow-up, months*	13.9	



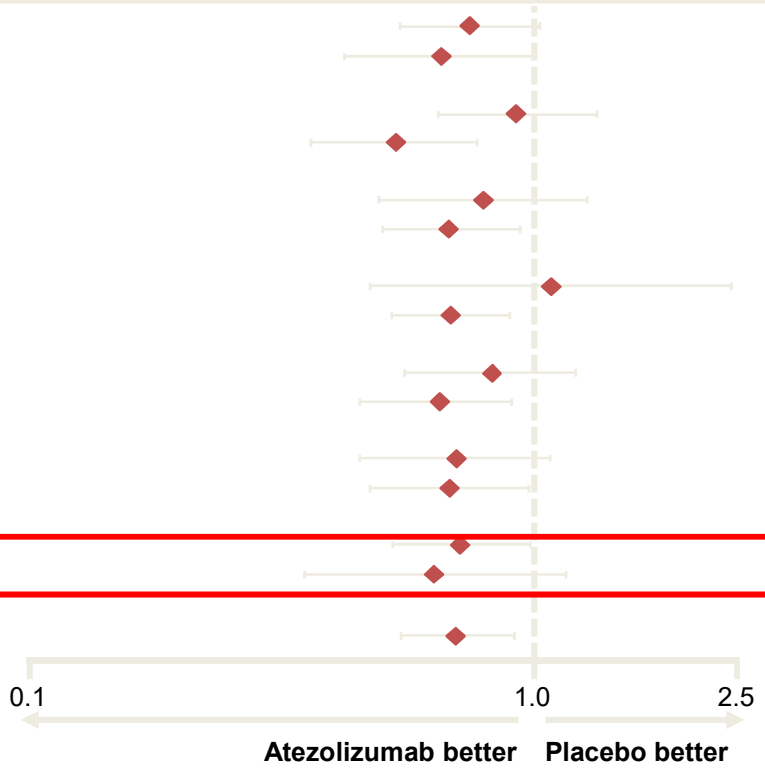
	Atezolizumab + CP/ET (N=201)	Placebo + CP/ET (N=202)
OS events, n (%)	104 (51.7)	134 (66.3)
Median OS, months (95% CI)	12.3 (10.8, 15.9)	10.3 (9.3, 11.3)
HR (95% CI)	0.70 (0.54, 0.91) p = 0.0069	
Median follow-up, months*	13.9	

Immune-related AEs — no. (%) > 1% Grade 3–4 AEs in either treatment group	Atezolizumab + CP/ET (N=196)			Placebo + CP/ET (N=196)		
	Grade 1–2	Grade 3–4	Grade 5	Grade 1–2	Grade 3–4	Grade 5
Rash	33 (16.7)	4 (2.0)	0	20 (10.2)	0	0
Hepatitis	11 (5.6)	3 (1.5)	0	9 (4.6)	0	0
Infusion-related reaction	7 (3.5)	4 (2.0)	0	9 (4.6)	1 (0.5)	0
Pneumonitis	3 (1.5)	1 (0.5)	0	3 (1.5)	2 (1.0)	0
Colitis	1 (0.5)	2 (1.0)	0	0	0	0
Pancreatitis	0	1 (0.5)	0	0	2 (1.0)	0

Horn et al: N Engl J Med 2018

ImPower133: Overall survival in key subgroups

Population	Median overall survival (months) Atezolizumab + CP/ET	Placebo + CP/ET	OS hazard ratio[a] (95% CI)
Male (n = 261)	12.3	10.9	0.74 (0.54, 1.02)
Female (n = 142)	12.5	9.5	0.65 (0.42, 1.00)
< 65 years (n = 217)	12.1	11.5	0.92 (0.64, 1.32)
≥ 65 years (n = 186)	12.5	9.6	0.53 (0.36, 0.77)
ECOG PS 0 (n = 140)	16.6	12.4	0.79 (0.49, 1.27)
ECOG PS 1 (n = 263)	11.4	9.3	0.68 (0.50, 0.93)
Brain metastases (n = 35)	8.5	9.7	1.07 (0.47, 2.43)
No brain metastases (n = 368)	12.6	10.4	0.68 (0.52, 0.89)
Liver metastases (n = 149)	9.3	7.8	0.81 (0.55, 1.20)
No liver metastases (n = 254)	16.8	11.2	0.64 (0.45, 0.90)
bTMB < 10 mut/mb (n = 139)	11.8	9.2	0.70 (0.45, 1.07)
bTMB ≥ 10 mut/mb (n = 212)	14.6	11.2	0.68 (0.47, 0.97)
bTMB < 16 mut/mb (n = 271)	12.5	9.9	0.71 (0.52, 0.98)
bTMB ≥ 16 mut/mb (n = 80)	17.8	11.9	0.63 (0.35, 1.15)
ITT (N = 403)	12.3	10.3	0.70 (0.54, 0.91)



- Clinical data cutoff date: April 24, 2018. bTMB (blood tumor mutational burden) assessed as reported in Gandara DR, et al. *Nat Med,* 2018.

[a] Hazard ratios are unstratified for patient subgroups and stratified for the ITT.

Horn et al: N Engl J Med 2018

Name	Study arms	Phase
LS-SCLC		
STIMULI	Nivolumab+ ipilimumab maintenance *vs.* observation	II
NCT02402920	Platinum/etoposide + radiation +/– pembrolizumab	I
ES-SCLC Treatment naïve		
REACTION	Platinum/etoposide +/– pembrolizumab	II
KEYNOTE 604	Platinum/etoposide +/– pembrolizumab	III
IMpower133	Carboplatin/etoposide +/– atezolizumab	III
Caspian	Platinum/etoposide+ durvalumab +/– tremelimumab *vs.* chemotherapy alone	III
MCC-18914	Platinum/etoposide followed by thoracic radiation +/– nivolumab +ipilimumab	I/II
NCT02402920	Platinum/etoposide followed by thoracic radiation +/– pembrolizumab	I
ES-SCLC Maintenance		
Checkmate 451	Nivolumab, nivolumab + ipilimumab, placebo	III
ES-SCLC Subsequent lines		
AFT17	Pembrolizumab *vs.* topotecan	II
Checkmate 331	Nivolumab *vs.* topotecan or amrubicin	III
IFCT-1603	Atezolizumab *vs.* topotecan or carboplatin/etoposide	II
MISP-MK3475	Pembrolizumab + paclitaxel	II
PembroPlus	Pembrolizumab + irinotecan	I/II
CA001-030	BMS-986012 +/– nivolumab	I/II
KEYNOTE 158	Pembrolizumab	II
NCT02937818	Durvalumab + tremelimumab *vs.* AZD1775+carboplatin	II
Winship 3112-15	Tremelimumab + durvalumab +/– radiation	II
M16-300	Nivolumab + rovalpituzumab +/– ipilimumab	I
AAAQ8257	SGI-110 followed by durvalumab + tremelimumab	I

ES-SCLC, extensive stage small cell lung cancer; LS, limited stage.

CPIs in SCLC: Where to from here?

1. Earlier

Stage I-III SCLC

- concurrent or maintenance?
- chemo + IO, or IO combination?

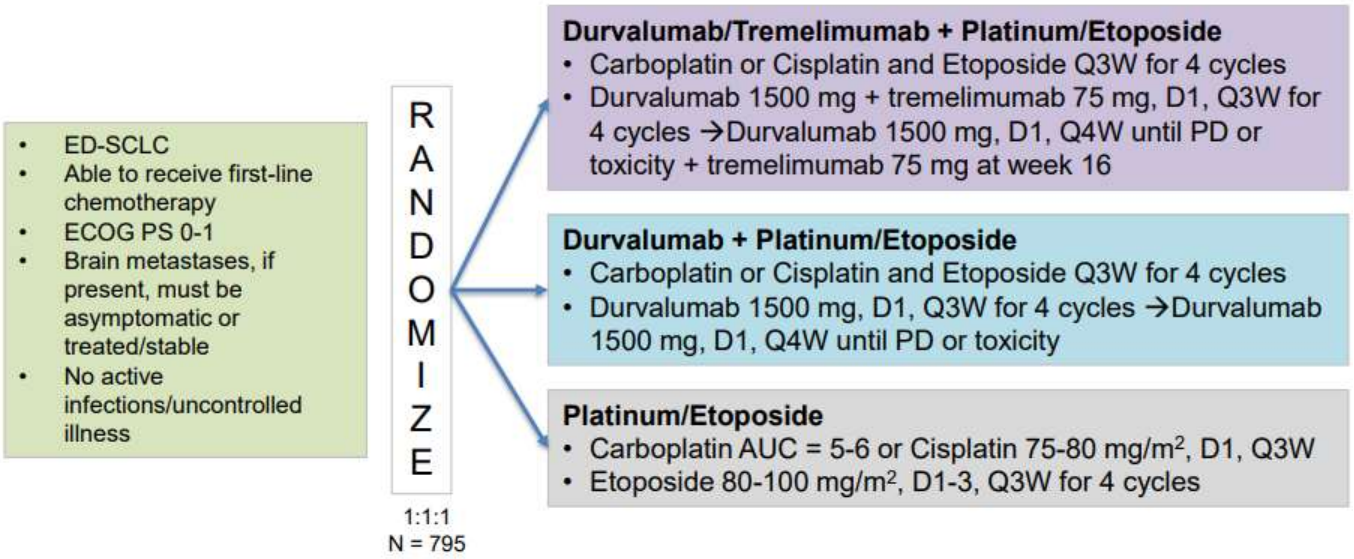
2. 1L Combinations + Chemotherapy

+ RT
+ PARP, DNA repair inhibition
+ Epigenetic modifiers
+ DLL3 targeted agents

3. Biomarker selection

- TMB
- PDL-1 composite proportion score
- Baseline autoantibodies?

CASPIAN: Chemo +/- Durva or Durva/Treme in ES-SCLC



- Co-primary endpoints: OS, PFS
- Secondary endpoints: ORR; 18-month OS; 6-, 12-month PFS, QoL, change in PS, PK
- Primary completion date: March 2019

6/27/2019 AstraZeneca announces positive overall survival (OS) results from the Phase III CASPIAN trial with *durvalumab+PE* in 1st-line extensive-stage small cell lung cancer

Summary: Emerging Role of Immunotherapy in SCLC

- SCLC appears to clinically be a good candidate for checkpoint immunotherapy (heavy smokers)
- SCLC is characterized by a high mutational load from tobacco carcinogens
- SCLC has unique immunologic features, in particular those associated with paraneoplastic syndromes
- Early studies showed long-term OS with PD-1 blockade or PD-1 blockade combined with anti-CTLA-1 therapy
- SCLC patients may be particularly at risk for autoimmune-related side effects
- Two Phase III trials have recently demonstrated improved OS with CPI+PE vs PE alone. This approach of CPI+PE now represents a new SOC in E-SCLC